JOC Article

pubs.acs.org/joc

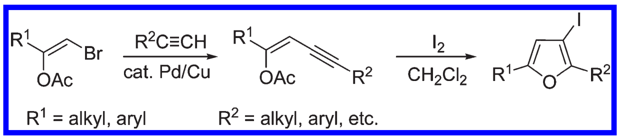
Synthesis of 2,5-Disubstituted 3-Iodofurans via Palladium-Catalyzed Coupling and Iodocyclization of Terminal Alkynes

Zhengwang Chen, Gao Huang, Huanfeng Jiang,* Huawen Huang, and Xiaoyan Pan

School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510640, P. R. China

jianghf@scut.edu.cn

Received December 4, 2010



2,5-Disubstituted 3-iodofurans are readily prepared under very mild reaction conditions by the palladium/copper-catalyzed cross-coupling of (*Z*)-*β*-bromoenol acetates and terminal alkynes, followed by iodocyclization. The useful intermediates conjugated enyne acetates are obtained in high yields in the transformation. Aryl- and alkyl-substituted alkynes undergo iodocyclization in good yields. The resulting iodine-containing furans can be readily elaborated to 2,3,5-trisubstituted furans.

Introduction

The synthesis of furans has attracted extensive interest, because they are found as key structural elements in numerous bioactive natural products and synthetic materials.[1] Moreover, they are useful intermediates for the preparation of a variety of heterocyclic and acyclic compounds.[2] Classical approaches to furan synthesis is the Paal−Knorr method in which 1,4-dicarbonyl compounds are converted to furan derivatives.[3] Recently, several studies have focused on the development of metal-catalyzed transformation, including the cyclization of alkynyl,[4] allenyl,[5] cyclopropyl,[6] and cyclopropenyl[7] ketone derivatives. Alternative strategies involve the cyclization of functionalized oxirane,[8] alkynols,[9] (*Z*)-2-en-4-yn-1-ols,[10] substituted propargyl vinyl ethers,[11] and others.[12]

(1) (a) Dean, F. M. *Naturally Occurring Oxygen Ring Compounds*; Butterworths: London, 1963; pp 1−28. (b) Donnelly, D. M. X.; Meegan, M. J. In *Comprehensive Heterocyclic Chemistry*; Katrizky, A. R., Ed.; Pergamon Press: New York, 1984; Vol. 4, pp 657−712. (c) Reid, S. T. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: New York, 1983; Vol. 33, pp 1−95.

(2) (a) Heaney, H.; Ahn, J. S. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, U.K., 1996; Vol. 2, pp 297−357. (b) Keay, B. A.; Dibble, P. W. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, U.K., 1996; Vol. 2, pp 395−436. (c) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991.

(3) (a) Benassi, R. In *Comprehensive Heterocyclic Chemistry*; Katrizky, A. R., Rees, C. W., Scriven, E. F., Eds.; Pergamon: New York, 1996; Vol. 2, p 259. (b) Dean, F. M.; Sargent, M. V. In *Comprehensive Heterocyclic Chemistry*; Katrizky, A. R., Rees, C. V., Eds.; Pergamon: New York, 1984; Vol. 3, p 531.

(4) For recent selected examples, see: (a) Zhang, Y.; Chen, Z.; Xiao, Y.; Zhang, J. *Chem.—Eur. J.* **2009**, *15*, 5208. (b) Liu, R.; Zhang, J. *Chem.—Eur. J.* **2009**, *15*, 9303. (c) Xiao, Y.; Zhang, J. *Chem. Commun.* **2009**, 3594. (d) Xiao, Y.; Zhang, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1903. (e) Zhang, J.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2006**, *45*, 6704. (f) Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164. (g) Sniady, A.; Durham, A.; Morreale, M. S.; Wheeler, K. A.; Dembinski, R. *Org. Lett.* **2007**, *9*, 1175. (h) Imagawa, H.; Kurisaki, T.; Nishizawa, M. *Org. Lett.* **2004**, *6*, 3679. (i) Patil, N. T.; Wu, H.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 4531. (j) Zhao, L.-B.; Guan, Z.-H.; Han, Y.; Xie, Y.-X.; He, S.; Liang, Y.-M. *J. Org. Chem.* **2007**, *72*, 10276. (k) Li, Y.; Yu, Z. *J. Org. Chem.* **2009**, *74*, 8904.

(5) For recent selected examples, see: (a) Ma, S.; Yu, Z. *Angew. Chem., Int. Ed.* **2002**, *41*, 1775. (b) Peng, L.; Zhang, X.; Ma, M.; Wang, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 1905. (c) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285. (d) Dudnik, A. S.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 5195. (e) Ma, S.; Zhang, J. *Chem. Commun.* **2000**, 117. (f) Sromek, A. W.; Rubina, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2005**, *127*, 10500. (g) Dudnik, A. S.; Xia, Y.; Li, Y.; Gevorgyan, V. *J. Am. Chem. Soc.* **2010**, *132*, 7645. (h) Zhou, C.-Y.; Chan, P. W. H.; Che, C.-M. *Org. Lett.* **2006**, *8*, 325. (i) Ma, S.; Li, L. *Org. Lett.* **2000**, *2*, 941.

(6) Ma, S.; Lu, L.; Zhang, J. *J. Am. Chem. Soc.* **2004**, *126*, 9645.

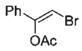
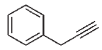
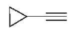
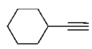
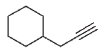
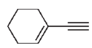
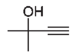
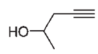
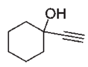
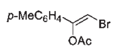
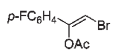
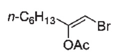
(7) (a) Ma, S.; Zhang, J. *J. Am. Chem. Soc.* **2003**, *125*, 12386. (b) Padwa, A.; Kassir, J. M.; Xu, S. L. *J. Org. Chem.* **1991**, *56*, 6971.

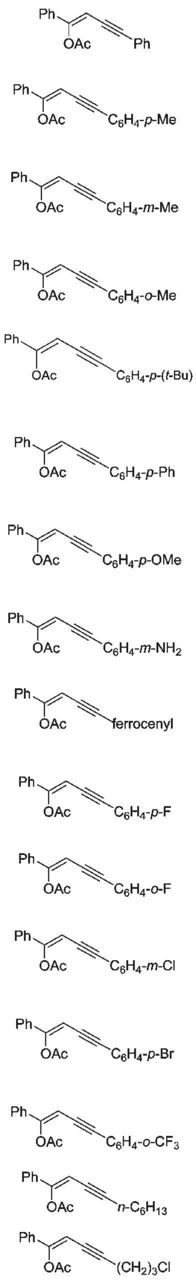
(8) (a) Hashmi, A. S. K.; Sinha, P. *Adv. Synth. Catal.* **2004**, *346*, 432. (b) Marshall, J. A.; DuBay, W. J. *J. Am. Chem. Soc.* **1992**, *114*, 1450. (c) Aurrecoechea, J. M.; Pérez, E.; Solay, M. *J. Org. Chem.* **2001**, *66*, 564. (d) Lo, C.-Y.; Guo, H.; Lian, J.-J.; Shen, F.-M.; Liu, R.-S. *J. Org. Chem.* **2002**, *67*, 3930. (e) Blanc, A.; Tenbrink, K.; Weibel, J.-M.; Pale, P. *J. Org. Chem.* **2009**, *74*, 4360. (f) Aurrecoechea, J. M.; Durana, A.; Pérez, E. *J. Org. Chem.* **2008**, *73*, 3650.

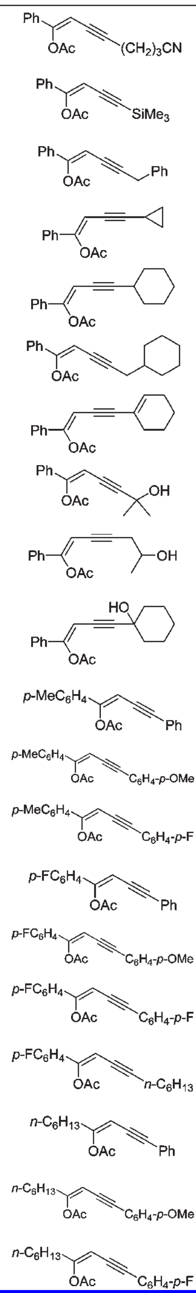
(9) (a) Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Milton, M. D.; Hidai, M.; Uemura, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 2681. (b) Arimitsu, S.; Hammond, G. B. *J. Org. Chem.* **2007**, *72*, 8559. (c) Nanayakkara, P.; Alper, H. *Adv. Synth. Catal.* **2006**, *348*, 545. (d) Pan, Y.; Zhao, S.; Ji, W.; Zhan, Z. *J. Comb. Chem.* **2009**, *11*, 103. (e) Egi, M.; Azechi, K.; Akai, S. *Org. Lett.* **2009**, *11*, 5002. (f) Aponick, A.; Li, C.-Y.; Malinge, J.; Marques, E. F. *Org. Lett.* **2009**, *11*, 4624.

Published on Web 01/14/2011 DOI: 10.1021/jo1023987

TABLE 1. Sonogashira Coupling of (*Z*)-*β*-Bromoenol Acetates and Terminal Alkynes[a]

entry	substrate	terminal alkyne	product	yield (%)
1	 **1**	PhC≡CH	**2**	93
2		*p*-MeC_6H_4C≡CH	**3**	90
3		*m*-MeC_6H_4C≡CH	**4**	88
4		*o*-MeC_6H_4C≡CH	**5**	83
5		*p*-(*t*-Bu)C_6H_4C≡CH	**6**	85
6		*p*-PhC_6H_4C≡CH	**7**	74
7		*p*-$MeOC_6H_4C$≡CH	**8**	83
8		*m*-$NH_2C_6H_4C$≡CH	**9**	78
9		FerrocenylC≡CH	**10**	81
10		*p*-FC_6H_4C≡CH	**11**	95
11		*o*-FC_6H_4C≡CH	**12**	88
12		*m*-ClC_6H_4C≡CH	**13**	92
13		*p*-BrC_6H_4C≡CH	**14**	94
14		*o*-$CF_3C_6H_4C$≡CH	**15**	84
15		*n*-$C_6H_{13}C$≡CH	**16**	72
16		$Cl(CH_2)_3C$≡CH	**17**	82
17		$NC(CH_2)_3C$≡CH	**18**	85
18		Me_3SiC≡CH	**19**	89
19			**20**	75
20			**21**	86
21			**22**	90
22			**23**	85
23			**24**	96
24			**25**	88
25			**26**	85
26			**27**	78
27	 **28**	PhC≡CH	**29**	90
28		*p*-$MeOC_6H_4C$≡CH	**30**	83
29		*p*-FC_6H_4C≡CH	**31**	96
30	 **32**	PhC≡CH	**33**	92
31		*p*-$MeOC_6H_4C$≡CH	**34**	90
32		*p*-FC_6H_4C≡CH	**35**	95
33		*n*-$C_6H_{13}C$≡CH	**36**	78
34	 **37**	PhC≡CH	**38**	84
35		*p*-$MeOC_6H_4C$≡CH	**39**	80
36		*p*-FC_6H_4C≡CH	**40**	89





[a]Reaction conditions: (*Z*)-*β*-bromoenol acetate (0.5 mmol), terminal alkyne (1.0 mmol), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), CuI (5 mol %), TEA (1 mmol) and THF (2 mL) solvent at 50 °C for 6 h.

Electrophilic cyclization of functionalized acetylene is one of the most attractive methods for constructing heterocycles, especially the iodo- and bromoheterocycles, which provide an opportunity for further functionalization through the transition-metal-catalyzed reactions. For example, a variety of heterocycles, including furans,[13] furanones,[14] benzofurans,[15] indoles,[16] benzothiophenes,[17] benzoselenophenes and selenophenes,[18] quinolines and isoquinolines,[19] isoxazoles,[20] etc.,[21] were obtained through the electrophilic cyclization in the past decades.

Very recently, we have communicated a convenient and expedient method for the synthesis of (*Z*)-*β*-haloenol acetates

(10) (a) Du, X.; Chen, H.; Liu, Y. *Chem.—Eur. J.* **2008**, *14*, 9495. (b) Zhang, X.; Lu, Z.; Fu, C.; Ma, S. *J. Org. Chem.* **2010**, *75*, 2589. (c) Gabriele, B.; Salerno, G.; Lauria, E. *J. Org. Chem.* **1999**, *64*, 7687. (d) Liu, Y.; Song, F.; Song, Z.; Liu, M.; Yan, B. *Org. Lett.* **2005**, *7*, 5409. (e) Schneider, C. C.; Caldeira, H.; Gay, B. M.; Back, D. F.; Zeni, G. *Org. Lett.* **2010**, *12*, 936.

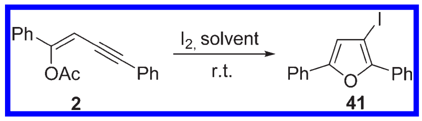
(11) (a) Jiang, H.; Yao, W.; Cao, H.; Huang, H.; Cao, D. *J. Org. Chem.* **2010**, *75*, 5347. (b) Suhre, M. H.; Reif, M.; Kirsch, S. F. *Org. Lett.* **2005**, *7*, 3925. (c) Cao, H.; Jiang, H.; Yao, W.; Liu, X. *Org. Lett.* **2009**, *11*, 1931. (d) Cao, H.; Jiang, H.; Yuan, G.; Chen, Z.; Qi, C.; Huang, H. *Chem.—Eur. J.* **2010**, *16*, 10553. (e) Cao, H.; Jiang, H.; Mai, R.; Zhu, S.; Qi, C. *Adv. Synth. Catal.* **2010**, *352*, 143.

from terminal alkynes using silver tetrafluoroborate as the catalyst.[22] Here we developed a two-step approach for the synthesis of 2,5-disubstituted 3-iodofurans involving the Sonogashira cross-coupling of terminal alkynes and (*Z*)-*β*-haloenol acetates, followed by iodocyclization. Although 2,5-disubstituted 3-iodofurans have been obtained previously from but-3-yn-1-ones[13a] or alk-3-yn-1,2-diols,[13b] readily accessible starting materials, the high efficiency and compatibility made our strategies attractive for furan synthesis. Moreover, it is noteworthy that the conjugated enyne acetate intermediates will be prove to have broad application.[23]

Results and Discussion

A two-step method to 2,5-disubstituted 3-iodofurans has been examined involving (i) the Sonogashira coupling of (*Z*)-*β*-bromoenol acetates with terminal alkynes to afford the conjugated enyne acetates and (ii) a iodocyclization reaction.

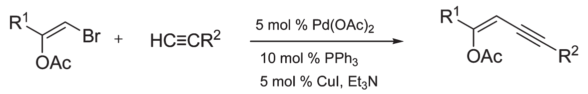
TABLE 2. Study of the Solvent Effect on the Iodocyclization Reaction[a]



entry	solvent	yield of **41**[b] (%)	recovery of **2** (%)
1	Et_2O	15	76
2	THF	28	67
3	MeCN	75	18
4	hexane	82	14
5	MeOH	tr	92
6[c]	$MeOH/CH_2Cl_2$	50	0
7	CH_2Cl_2	94	0

[a]Reaction conditions: **2** (0.25 mmol), I_2 (1.5 equiv), and $NaHCO_3$ (1.5 equiv) in 2 mL of solvent at rt for 8 h. [b]Yields of **41** are given for isolated products. [c]1 mL of MeOH and 1 mL of CH_2Cl_2.

To test the scope of this overall approach, we first studied the Sonogashira reaction of (*Z*)-*β*-bromoenol acetates with terminal alkynes. Treatment of (*Z*)-*β*-bromoenol acetates bearing different functionalities with a wide range of terminal alkynes under standard Sonogashira coupling conditions (0.5 mmol of (*Z*)-*β*-bromoenol acetate, 2.0 equiv of terminal alkyne, 5 mol % of $Pd(OAc)_2$, 10 mol % of PPh_3, 5 mol % of CuI, 1 mmol of Et_3N, and 2 mL of THF at 50 °C for 6 h) affords high yields of the target products (eq 1, Table 1).



(1)

With the standard conditions in hand, the scope of both (*Z*)-*β*-bromoenol acetates and terminal alkynes was explored for the coupling reaction (Table 1). Initially, a variety of terminal alkynes were investigated by reacting with (*Z*)-2-bromo-1-phenylvinyl acetate (**1**) (entries 1−26). The results showed that the aromatic alkynes with either an electron-donating or electron-withdrawing group on the benzene ring were able to generate the corresponding products in good to excellent yields (entries 1−14). Substitution at the *ortho* position of the aromatic ring had some impact on the yields (entries 2−4, 11, and 12). It is noteworthy that ethynylferrocene and the 3-ethynylbenzenamine also afford the corresponding coupling products in good yields (entries 8 and 9). It should be pointed out that the carbon−halogen bonds tolerated the substrate reactivity and the halogen-containing products were afforded smoothly (entries 12 and 13). The alkyl alkynes were also found to be suitable substrates for the standard conditions (entries 15−26). When the aliphatic alkynes bearing chloro, cyano, silyl, benzylic, cyclopropyl, cyclohexyl, vinylic, and hydroxyl groups were employed, the reaction proceeded in good to excellent yields. Subsequently, some representative (*Z*)-*β*-bromoenol acetates were examined, and high yields were obtained in almost all case, regardless of the nature of terminal alkynes (entries 27−36).

The starting conjugated enyne acetates were readily available through the Sonogashira coupling reaction, and we then focused on the development of an optimum conditions of the iodocyclization (Table 2). The reaction of (*Z*)-1,4-diphenylbut-1-en-3-ynyl acetate (**2**) with iodine and $NaHCO_3$ was chosen as a model system for this process. The reaction showed a strong solvent dependence. Good yields were

(12) (a) Zhang, M.; Jiang, H.-F.; Neumann, H.; Beller, M.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2009**, *48*, 1681. (b) Barluenga, J.; Riesgo, L.; Vicente, R.; López, L. A.; Tomás, M. *J. Am. Chem. Soc.* **2008**, *130*, 13528. (c) Xu, B.; Hammond, G. B. *J. Org. Chem.* **2006**, *71*, 3518. (d) Xu, L.; Huang, X.; Zhong, F. *Org. Lett.* **2006**, *8*, 5061. (e) Donohoe, T. J.; Fishlock, L. P.; Lacy, A. R.; Procopiou, P. A. *Org. Lett.* **2007**, *9*, 953. (f) Liu, W.; Jiang, H.; Zhang, M.; Qi, C. *J. Org. Chem.* **2010**, *75*, 966. (g) Li, H.; Hsung, R. P. *Org. Lett.* **2009**, *11*, 4462. (h) Sydnes, L. K.; Holmelid, B.; Sengee, M.; Hanstein, M. *J. Org. Chem.* **2009**, *74*, 3430. (i) Yang, Y.-K.; Choi, J.-H.; Tae, J. *J. Org. Chem.* **2005**, *70*, 6995.

(13) (a) Sniady, A.; Wheeler, K, A.; Dembinski, R. *Org. Lett.* **2005**, *7*, 1769. (b) Bew, S. P.; Knight, D. W. *Chem. Commun.* **1996**, 1007. (c) Liu, Y.; Zhou, S. *Org. Lett.* **2005**, *7*, 4609. (d) Yao, T.; Zhang, X.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 7679. (e) Arimitsu, S.; Jacobsen, J. M.; Hammond, G. B. *J. Org. Chem.* **2008**, *73*, 2886.

(14) (a) Crone, B.; Kirsch, S. F. *J. Org. Chem.* **2007**, *72*, 5435. (b) Just, Z. W.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 2662.

(15) (a) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 10292. (b) Manarin, F.; Roehrs, J. A.; Gay, R. M.; Brandão, R.; Menezes, P. H.; Nogueira, C. W.; Zeni, G. *J. Org. Chem.* **2009**, *74*, 2153. (c) Okitsu, T.; Nakazawa, D.; Taniguchi, R.; Wada, A. *Org. Lett.* **2008**, *10*, 4967. (d) Cho, C.-H.; Neuenswander, B.; Lushington, G. H.; Larock, R. C. *J. Comb. Chem.* **2008**, *10*, 941.

(16) (a) Barluenga, J.; Trincado, M.; Rubio, E.; González, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2406. (b) Yue, D.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1037. (c) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 62.

(17) (a) Yue, D.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 1905. (b) Flynn, B. L.; Verdier-Pinard, P.; Hamel, E. *Org. Lett.* **2001**, *3*, 651.

(18) (a) Kesharwani, T.; Worlikar, S. A.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 2307. (b) Alves, D.; Luchese, C.; Nogueira, C. W.; Zeni, G. *J. Org. Chem.* **2007**, *72*, 6726.

(19) (a) Zhang, X.; Campo, M. A.; Yao, T.; Larock, R. C. *Org. Lett.* **2005**, *7*, 763. (b) Huang, Q.; Hunter, J. A.; Larock, R. C. *Org. Lett.* **2001**, *3*, 2973. (c) Huang, Q.; Hunter, J. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 3437.

(20) (a) Waldo, J. P.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 9643. (b) Waldo, J. P.; Larock, R. C. *Org. Lett.* **2005**, *7*, 5203.

(21) For recent selected examples, see: (a) Barluenga, J.; Trincado, M.; Marco-Arias, M.; Ballesteros, A.; Rubio, E.; González, J. M. *Chem. Commun.* **2005**, 2008. (b) Barluenga, J.; Vázquez-Villa, H.; Ballesteros, A.; González, J. M. *J. Am. Chem. Soc.* **2003**, *125*, 9028. (c) Yue, D.; Cà, N. D.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1581. (d) Arcadi, A.; Cacchi, S.; Giuseppe, S. D.; Fabrizi, G.; Marinelli, F. *Org. Lett.* **2002**, *4*, 2409. (e) Peng, A.-Y.; Ding, Y.-X. *Org. Lett.* **2004**, *6*, 1119. (f) Yao, T.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 5936. (g) Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 1432. (h) Zhang, X.; Sarkar, S.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 236. (i) Worlikar, S. A.; Kesharwani, T.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 1347. (j) Zhou, C.; Dubrovsky, A. V.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 1626.

(22) Chen, Z.; Li, J.; Jiang, H.; Zhu, S.; Li, Y.; Qi, C. *Org. Lett.* **2010**, *12*, 3262.

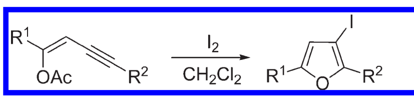
(23) For selective examples of enyne derivatives, see: (a) Li, Y.; Liu, X.; Jiang, H.; Feng, Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 3338. (b) Nakao, Y.; Hirata, Y.; Tanaka, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 385. (c) Shirakawa, E.; Yoshida, H.; Kurahashi, T.; Nakao, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1998**, *120*, 2975. (d) Suginome, M.; Shirakura, M.; Yamamoto, A. *J. Am. Chem. Soc.* **2006**, *128*, 14438. (e) Liu, Y.; Zhong, Z.; Nakajima, K; Takahashi, T. *J. Org. Chem.* **2002**, *67*, 7451. (f) Yoshida, H.; Shirakawa, E.; Kurahashi, T.; Nakao, Y.; Hiyama, T. *Organometallics* **2000**, *19*, 5671.

TABLE 3. Synthesis of 3-Iodofurans[a]

entry	alkyne	product	yield (%)
1	**2**	**41**	94
2	**3**	**42**	94
3	**4**	**43**	95
4	**5**	**44**	86
5	**6**	**45**	92
6	**7**	**46**	93
7	**8**	**47**	85
8	**9**	**48**	n.p.
9	**10**	**49**	n.p.
10	**11**	**50**	92
11[b]	**12**	**51**	86
12	**13**	**52**	93
13	**14**	**53**	94
14	**15**	**54**	95
15	**16**	**55**	85
16	**17**	**56**	78
17	**18**	**57**	85
18	**19**	**58**	n.p.
19	**20**	**59**	78
20	**21**	**60**	n.p.
21	**22**	**61**	88
22	**23**	**62**	90
23	**24**	**63**	n.p.
24	**25**	**64**	n.p.
25	**29**	**65**	98
26	**30**	**66**	95
27	**31**	**67**	97
28	**33**	**68**	98
29	**34**	**69**	93
30	**35**	**70**	90
31	**36**	**71**	80
32	**38**	**72**	95

[a]Reaction conditions: enyne acetate (0.25 mmol), I_2 (1.5 equiv), and $NaHCO_3$ (1.5 equiv) in 2 mL of CH_2Cl_2 at rt for 8 h. [b]Reacted for 24 h.

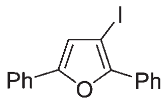
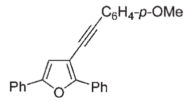
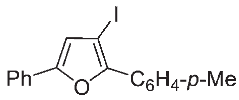
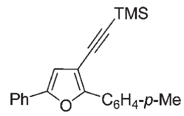
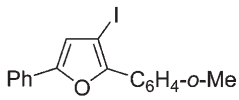
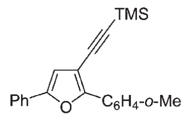
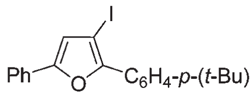
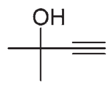
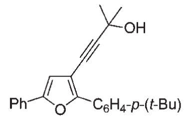
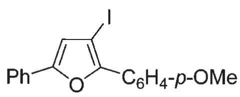
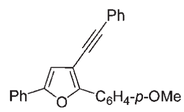
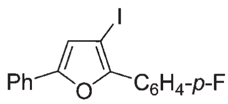
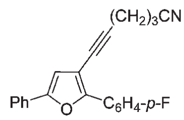
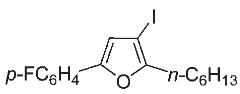
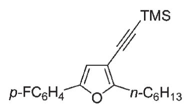
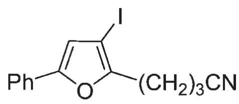
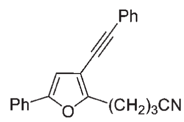
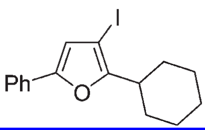
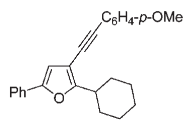
obtained when MeCN and hexane were used; better results were achieved using CH_2Cl_2, which furnished the desired products **41** in 94% yield.



(2)

To test the scope of this iodocyclization reaction, we subjected a number of enyne acetates to the reaction conditions (eq 2, Table 3). In general, most of the substrates could afford the corresponding 2,5-disubstituted 3-iodofurans in excellent yields. Initially, a set of substituents at the terminal alkyne moiety were evaluated in the standard conditions (entries 1−24). The results indicated that substituted aryl groups were perfectly tolerated besides the substrate **8** and **9** (entries 1−14) . The alkyne **6** bearing a bulky *tert*-butyl group afforded a high yield of the desired furan (entry 5). Substitution at the 2-position of the aromatic ring had a slight impact, and the alkyne **12** required prolonged reaction time (entries 4 and 11). The chloro and bromoaryl group were tolerated in this transformation and therefore available for additional functionalization of the product at the C−Cl or C−Br bond (entries 12 and 13). As the challenging substrates, aliphatic terminal alkyne moieties were compatible with the reaction system. The iodocyclization process accommodates a variety of functional groups including

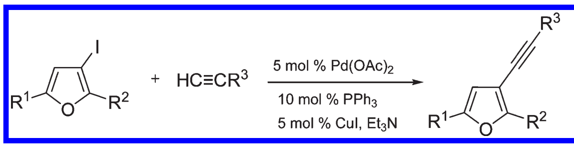
TABLE 4. Sonogashira Coupling of 3-Iodofurans and Terminal Alkynes[a]

entry	3-iodofuran		terminal alkyne	product		yield (%)
1		**41**	p-MeOC$_6$H$_4$C≡CH		**73**	92
2		**42**	Me$_3$SiC≡CH		**74**	94
3		**44**	Me$_3$SiC≡CH		**75**	88
4		**45**			**76**	85
5		**47**	PhC≡CH		**77**	95
6		**50**	NC(CH$_2$)$_3$C≡CH		**78**	89
7		**71**	Me$_3$SiC≡CH		**79**	92
8		**57**	PhC≡CH		**80**	90
9		**61**	p-MeOC$_6$H$_4$C≡CH		**81**	93

[a]Reaction conditions: 2,5-disubstituted 3-iodofuran (0.1 mmol), terminal alkyne (0.2 mmol), Pd(OAc)$_2$ (5 mol %), PPh$_3$ (10 mol %), CuI (5 mol %), TEA (1.2 mmol), and THF (1 mL) solvent at rt for 6 h.

halides, nitriles, cyclohexyl, and benzylic on the alkyne moiety (entries 16, 17, 19, 21, and 22). Interestingly, the nature of the R^1 group on the double bond had very little effect on the reaction rate or the product yield (entries 25−32). Unfortunately, some substrates failed to afford the desired furans under our standard conditions (entries 8, 9, 18, 20, 23, and 24). It appeared that the nature of the substituents attached to the triple bond has a major impact on the success of the reaction.

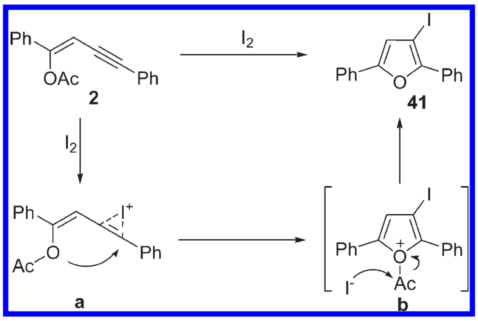
The resulting product 2,5-disubstituted 3-iodofurans appeared attractive as intermediates for the preparation of more highly functionalized furans. To further the utility of our methodology, we studied the Sonogashira coupling reaction of 2,5-disubstituted 3-iodofurans with terminal alkynes (eq 3, Table 4). As shown in Table 4, all of the substrates reacted well and provided excellent yields of the desired coupling products. Moreover, compounds **74**, **75**, **76**, and **79** were easily transformed to the functionalized terminal alkynes.[24,25]



(3)

A possible mechanism was proposed on the basis of the previous work mechanism and our reaction results

SCHEME 1



(Scheme 1).[16b,18b,21d] In the first step, coordination of the triple bond to the I_2 generates the iodonium **a**, then an anti attack of the electrophile forms **b**, and subsequently the acetyl group can be removed from intermediate **b** with aid of an nucleophile to afford the target produce **41**.

Conclusions

A very efficient synthesis of 2,5-disubstituted 3-iodofurans has been developed through the Sonogashira coupling of (*Z*)-*β*-bromoenol acetates with terminal alkynes, followed by intramolecular iodocyclization. The useful intermediates of conjugate enyne acetates were obtained in high yields with broad functional groups tolerated. We observed that the iodocyclization was sensitive to the nature of the solvent and the structure of conjugate enyne acetates. The 2,5-disubstituted 3-iodofurans appear attractive for the prearation of more highly substituted furans. For example, the 2,3,5-trisubstituted furans were prepared with excellent yields.

Experimental Section

General Procedure for Synthesis of (*Z*)-1,4-Disubstitutedbut-1-en-3-ynyl Acetates. To the mixture of (*Z*)-*β*-bromoenol acetate (0.5 mmol), $Pd(OAc)_2$ (5 mol %), and PPh_3 (10 mol %) in THF (2 mL) solvent, were added successively TEA (1 mmol) and CuI (5 mol %), the mixture was stirred for 5 min at rt, terminal alkyne (1.0 mmol) was added, the flask was then sealed, and the mixure was stirred at 50 °C for 6 h. The solution was washed with water and extracted with ethyl acetate (3 × 15 mL), and the combined extract was dried with anhydrous $MgSO_4$. Solvent was removed, and the residue was separated by column chromatography to give the pure sample.

(24) (a) Carpita, A.; Mannocci, L.; Rossi, R. *Eur. J. Org. Chem.* **2005**, 1859. (b) Dabdoub, M. J.; Baroni, A. C. M.; Lenardão, E. J.; Gianeti, T. R.; Hurtado, G. R. *Tetrahedron* **2001**, *57*, 4271.

(25) (a) Ji, S.; Yang, J.; Yang, Q.; Liu, S.; Chen, M.; Zhao, J. *J. Org. Chem.* **2009**, *74*, 4855. (b) Gagnon, E.; Rochefort, A.; Métivaud, V.; Wuest, J. D. *Org. Lett.* **2010**, *12*, 380. (c) Wu, X. H.; Jin, S.; Liang, J. H.; Li, Z. Y.; Yu, G.; Liu, S. H. *Organometallics* **2009**, *28*, 2450. (d) Mao, G.; Orita, A.; Matsuo, D.; Hirate, T.; Iwanaga, T.; Toyota, S.; Otera, J. *Tetrahedron Lett.* **2009**, *50*, 2860.

(*Z*)-1,4-Diphenylbut-1-en-3-ynyl Acetate (2). This product was obtained as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47−7.49 (m, 2H), 7.41−7.44 (m, 2H), 7.33−7.37 (m, 3H), 7.30−7.32 (m, 3H), 6.15 (s, 1H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 155.2, 133.0, 131.0, 129.1, 128.2, 127.9, 127.8, 124.1, 122.7, 97.3, 96.5, 83.6, 20.1. MS (EI) *m*/*z*: 77, 105, 115, 191, 220, 262. Anal. Calcd for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 82.27; H, 5.45.

General Procedure for Iodocyclization. A mixture of (*Z*)-1,4-disubstitutedbut-1-en-3-ynyl acetate (0.25 mmol), I_2 (1.5 equiv) and $NaHCO_3$ (1.5 equiv) in CH_2Cl_2 (2 mL) was stirred at rt for 8 h unless otherwise specified. The excess I_2 was removed by washing with a saturated aqueous solution of $Na_2S_2O_3$. The solution was extracted with ethyl acetate (3 × 10 mL), and the combined extract was dried with anhydrous $MgSO_4$. Solvent was removed, and the residue was separated by column chromatography to give the pure sample.

3-Iodo-2,5-diphenylfuran (41). This product was obtained as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, J = 8.0 Hz, 2H), 7.68 (d, J = 7.6 Hz, 2H), 7.27−7.46 (m, 6H), 6.83 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.9, 151.0, 130.1, 129.5, 128.7, 128.4, 128.1, 128.0, 126.1, 123.8, 115.7, 62.7. MS (EI) *m*/*z*: 77, 105, 189, 191, 346. Anal. Calcd for $C_{16}H_{11}IO$: C, 55.51; H, 3.20. Found: C, 55.34; H, 3.28.

General Procedure for the Preparation of 2,3,5-Trisubstituted Furans. To the mixture of 2,5-disubstituted 3-iodofuran (0.1 mmol), $Pd(OAc)_2$ (5 mol %) and PPh_3 (10 mol %) in THF (2 mL) solvent were added successively TEA (0.2 mmol) and CuI (5 mol %), the mixture was stirred for 5 min at rt, terminal alkyne (0.2 mmol) was added, the flask was then sealed, and the mixture was stirred at rt for 6 h. The solution was washed with water and extracted with ethyl acetate (3 × 5 mL), and the combined extract was dried with anhydrous $MgSO_4$. Solvent was removed, and the residue was separated by column chromatography to give the pure sample.

3-(2-(4-Methoxyphenyl)ethynyl)-2,5-diphenylfuran (73). This product was obtained as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, J = 7.6 Hz, 2H), 7.73 (d, J = 7.6 Hz, 2H), 7.39−7.51 (m, 6H), 7.28−7.33 (m, 2H), 6.90 (d, J = 8.8 Hz, 2H), 6.82 (s, 1H), 3.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 153.6, 152.2, 132.9, 130.5, 130.0, 128.8, 128.6, 127.9, 127.9, 124.7, 123.9, 115.2, 114.1, 110.0, 105.2, 94.0, 81.3, 55.3. MS (EI) *m*/*z*: 51, 77, 152, 199, 277, 350. Anal. Calcd for $C_{25}H_{18}O_2$: C, 85.69; H, 5.18. Found: C, 85.43; H, 5.25.

Acknowledgment. We gratefully acknowledge the National Natural Science Foundation of China (Nos. 20625205, 20772034, and 20932002), National Basic Research Program of China (973 Program) (No. 2011CB808600), Doctoral Fund of Ministry of Education of China (20090172110014), and Guangdong Natural Science Foundation (No. 10351064101000000) for financial support.

Supporting Information Available: Full experimental details and copies of NMR spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.